Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2024;13(2):326-31

Comparison of single and combination risk factors in pancreatic ductal adenocarcinoma with control and benign hepatobiliary disease groups

Zeynep Kucukakcali, Ipek Balikci Cicek

İnönü University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Malatya, Türkiye

Received 28 November 2023; Accepted 14 February 2024
Available online 31 May 2024 with doi: 10.5455/medscience.2023.11.225

Abstract

Pancreatic cancer is one of the most common solid tumours and pancreatic ductal adenocarcinomas (PDACs) are the most common type of pancreatic cancer, accounting for 95% of cases. The aim of this study was not to analyze the risk factors that may be associated with PDAC, the most common type of pancreatic cancer, but to determine how these factors, taken together, affect the diagnosis of the disease. An open-access dataset containing PDAC and associated factors was used in the study. Mann Whitney U test was used in data analysis. ROC analysis was used to determine the power of the variables individually and together, in discriminating PDAC. According to the results of ROC analysis for control-PDAC and benign hepatobiliary disease-PDAC groups, the discriminatory power of the creatinine variable between the groups was found to be quite low (AUC control-PDAC=0.531, AUC benign hepatobiliary disease-PDAC=0.514, respectively). The AUC values obtained from LYVE1, REG1B, TFF1 variables for control-PDAC and benign hepatobiliary disease-PDAC comparisons are high and the discriminative power of the variables is said to be high. The results of ROC analyses performed with variables obtained from binary and triple combinations of these variables were also found to be quite high. Based on the findings presented in the article, it can be concluded that the individual components connected with the disease, when utilized in isolation for diagnostic purposes, exhibit low impact. However, when these aspects are collectively included, there is an observed enhancement in diagnostic accuracy. Hence, it is advisable to collectively evaluate the elements believed to be linked with the disease during the diagnostic process, as this approach may yield more precise outcomes.

Keywords: Pancreatic cancer, pancreatic ductal adenocarcinoma, variable combination, diagnosis

Introduction

Pancreatic cancer has the poorest prognosis among frequently recognized solid tumors, with a 5-year overall survival (OS) rate of about 10% [1]. With this survival rate, it is seen that the patients' chances of survival are very poor, and the number of deaths from this disease continues to rise on a daily basis. According to reports, the current spike in pancreatic cancer has overshadowed breast cancer, which ranks third in cancer mortality [2]. Pancreatic ductal adenocarcinomas (PDAC) are the most common kind of pancreatic cancer, accounting for 95% of cases. PDACs are exocrine cell tumors that have a high death rate. Endocrine pancreatic cancers, on the other hand, develop more slowly and have a better prognosis than exocrine pancreatic tumours [3].

The high death rate in PDAC is caused by four major reasons. The first is related to the location of the pancreas in the body. The pancreas is an organ in the upper abdomen, behind the stomach, between the aorta and the upper abdominal branches. Not only is it difficult to identify tumors due to its position, but also the malignant region typically grows around these vessels, only 15%-20% of patients are acceptable for surgical excision based on curative therapy [4]. The second reason is that PDAC spreads quickly and has an aggressive nature. At the time of admission, more than half of the patients have distant metastatic disease, and the majority of patients receiving resection have metastases within 4 years of surgery. Individuals with seemingly confined malignancies are considered to have micrometastases in this situation [1,5,6]. The third explanation is that the physiological repercussions of PDAC

CITATION
Kucukakcali Z, Balikci Cicek I. Comparison of single and combination risk factors in pancreatic ductal adenocarcinoma with control and benign hepatobiliary disease groups. Med Science. 2024;13(2):326-31.

Corresponding Author: Zeynep Kucukakcali, İnönü University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Malatya, Türkiye
Email: zeynep.tunc@inonu.edu.tr

DOI: 10.5455/medscience.2023.11.225

significantly weaken patients by decreasing their resilience to intensive therapy. At the time of diagnosis, up to 80% of PDAC patients exhibit cachexia fatigue syndrome, which is worsened by exocrine and endocrine pancreatic dysfunction [7-9]. The final key aspect is that PDAC can advance fast even when treated with the most potent systemic medicines and radiation, and it exhibits considerable resistance to various antineoplastic therapies with extremely poor response rates [10]. PDAC, like other tumor types, is eligible for several trials with targeted medicines, however the results were disappointing [11,12].

For PDAC, which is a highly metastastic disease detected late, treatment in the early stages may be beneficial [13]. When the disease can be detected in the early stages and treatment can be started as soon as possible, the 5-year survival rate can increase from 10% to 32% [14]. Therefore, early diagnosis is very important for the disease. However, there are very few useful biomarkers that can detect the disease at early stages. In some studies, the use of CA19-9 has been suggested for early stage detection, however it has not reached clinically conclusive results [13,15]. Therefore, different biomarkers are recuired for the detection of the disease.

Therefore, in this study, it was aimed to determine how effective they are in the diagnosis of PDAC by examining the relationship of the protein, which is thought to be effective for the detection of patients with PDAC, with the help of ROC analysis. In addition to analysing these parameters individually, it was also aimed to investigate their effects on PDAC by taking their combinations. Thus, it will be possible to determine whether the evaluation of the parameters together is effective in the differentiation of PDAC and whether the evaluation of the parameters together gives better results.

Material and Methods

Data Set and Features

The dataset used in the study is an open access dataset created to identify individuals with pancreatic cancer. This data set was obtained from "https://www.kaggle.com/datasets/johnjdavisiv/urinary-biomarkers-for-pancreatic-cancer" and is open to the use of researchers. For pancreatic cancer detection, healthy controls, patients with non-cancerous pancreatic disorders such as chronic pancreatitis, patients with pancreatic ductal adenocarcinoma and their data were used. Plasma_CA19_9, creatinine, LYVE1, REG1B, TFF1, REG1A variables were used as independent variables in the study. Among these variables, plasma_CA19_9 and REG1A contain high missing values.

Explanations for the 4 variables creatinine, LYVE1, REG1B, TFF1, which do not contain missing values, are given below.

- Creatinine is a protein that is often used as an indicator of kidney function,
- LYVE1 is lymphatic vessel endothelial hyaluronan receptor 1, a protein that may play a role in tumor metastasis,
- REG1B is a protein that may be associated with pancreas regeneration,
- TFF1 is trefoil factor 1, which may be related to regeneration and repair of the urinary tract.

Statistical Analysis

Descriptive statistics for the continuous variables were presented as Median and 95% Confidence interval. Normality of continuous variables was tested by Kolmogorov-Smirnov test. According to whether providing of normality assumption, Mann-Whitney U test was used to compare independent groups. In addition, ROC analysis was performed to determine the extent to which the explanatory variables discriminate the target variable. In order to examine the effects of the combinations of variables with good discrimination power on the target variable as a result of ROC analysis, predictive probability values of the combinations of variables were calculated using logistic regression. Statistical significance level was considered as 5% and IBM SPSS 26.00 statistical program was used for all statistical computations.

Results

There were 590 individuals in the study and 299 of them were female and 291 of them were male. The mean age was 59.08±13.11 years. Of the individuals in the data set, 183 were controls, 208 had benign hepatobiliary disease and 199 had pancreatic ductal adenocarcinoma. The mean age was 56.33±12.20 years in the control group, 54.70±13.34 years in the benign hepatobiliary disease group and 66.8±10.50 years in the pancreatic ductal adenocarcinoma group. There were 115 women and 68 men in the control group, 101 women and 107 men in the benign hepatobiliary disease group, 83 women and 116 men in the pancreatic ductal adenocarcinoma group.

Plasma_CA19_9, REG1A variables, which are included in the data set and have a high rate of missing values, were included in the statistical analyses. Statistical analyses were performed with the other variables creatinine, LYVE1, REG1B, TFF1.

Comparison of Control and Pancreatic Ductal Adenocarcinoma Patients

When control and pancreatic ductal adenocarcinoma patients were compared in terms of creatinine, LYVE1, REG1B, TFF1, significant differences were obtained between the 2 groups in all variables except for the creatinine. The results of the analyzes are given in Table 1.

The results of the ROC analysis with the variables were given in Figure 1 and Table 2.

When the results of the ROC analysis are analyzed, it is seen that the creatinine variable could not discriminating the categories of the target variable, and the other variables provided distinction.

According to the results of ROC analysis, the results of ROC analysis using the combinations of LYVE1, REG1B, TFF1 variables which are successful in discriminating the categories of target variable are given in Figure 2 and Table 3.

When the results of the ROC analysis for the combinations

DOI: 10.5455/medscience.2023.11.225

were analysed, it was observed that the discrimination power of the REG1B variable, which was the variable with the lowest discrimination power, increased with the combinations, and taking the combinations of the variables and evaluating them together increased the discrimination power. The result obtained from the combination of 3 variables is 0.907 and it is important to evaluate the variables together on the categories of the target variable.

Table 1. Comparison of control and pancreatic ductal adenocarcinoma patients in terms of variables

Variables	Diagnosis		p*
	Control	Pancreatic ductal adenocarcinoma	
	Median (95% confidence interval for median)		
Creatinine	0.713 (0.599-0.86)	0.724 (0.622-0.826)	0.293
LYVE1	0.146 (0.022-0.571)	5.621 (5.133-6.063)	<0.001
REG1B	17.583 (13.101-24.774)	123.105 (104.849-156.241)	<0.001
TFF1	59.793 (33.307-95.767)	722.523 (610.899-869.566)	<0.001

*:Mann Whitney U test

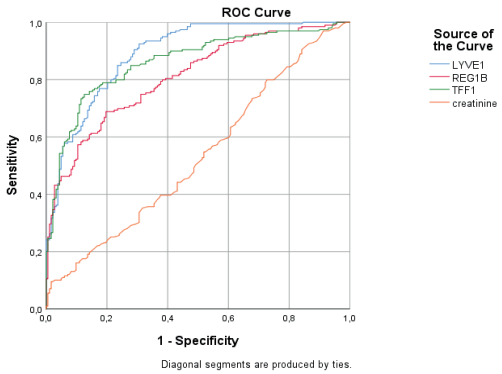

Figure 1. Graph of ROC analysis results for control and pancreatic ductal adenocarcinoma patients

Table 2. Result of ROC analysis for control and pancreatic ductal adenocarcinoma patients

Test result variable (s)	Area under the curve (AUC)
Creatinine	0.531
LYVE1	0.891
REG1B	0.810
TFF1	0.862

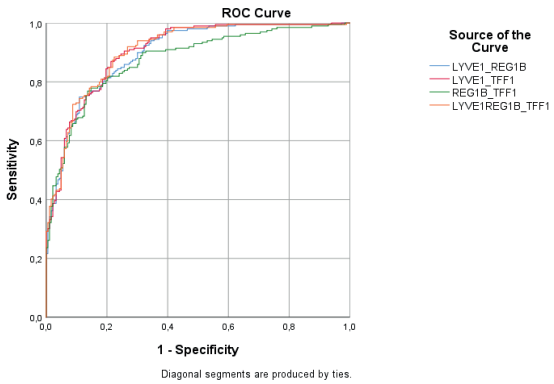

Figure 2. Graph of ROC analysis results for combinations in control and pancreatic ductal adenocarcinoma patients

Table 3. Result of ROC analysis for combinations in control and pancreatic ductal adenocarcinoma patients

Test result variable (s)	Area under the curve (AUC)
LYVE1_REG1B	0.898
LYVE1_TFF1	0.905
REG1B_TFF1	0.876
LYVE1_REG1B_TFF1	0.907

Comparison of Control and Benign Hepatobiliary Disease Patients

When benign hepatobiliary disease patients and pancreatic ductal adenocarcinoma patients were compared in terms of creatinine, LYVE1, REG1B, TFF1, significant differences were obtained between the 2 groups in all variables except for the creatinine. The results of the analyzes are given in Table 4.

The results of the ROC analysis with the variables were given in Figure 3 and Table 5.

When the results of the ROC analysis are analyzed, it is seen that the creatinine variable could not discriminating the categories of the target variable, and the other variables provided distinction.

According to the results of ROC analysis, the results of ROC analysis using the combinations of LYVE1, REG1B, TFF1 variables which are successful in discriminating the categories of target variable are given in Figure 4 and Table 6.

When the results of ROC analysis with combinations are analysed, it is seen that the power of binary and triple combinations of variables in discriminating the target variable does not increase much compared to the results of single ROC analysis. for benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients' groups, the evaluation of variables together was not effective.

DOI: 10.5455/medscience.2023.11.225

Table 4. Comparison of benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients in terms of variables

Variables	Diagnosis		p*
	Control	Pancreatic ductal adenocarcinoma	
	Median (95% confidence interval for median)		
Creatinine	0.746 (0.656-0.826)	0.724 (0.622-0.826)	0.637
LYVE1	1.212 (0.797-1.474)	5.621(5.133-6.063)	<0.001
REG1B	20.155 (15.753-28.145)	123.105 (104.849-156.241)	<0.001
TFF1	210.213 (140.046-310.29)	722.523 (610.899-869.566)	<0.001

*:Mann Whitney U test

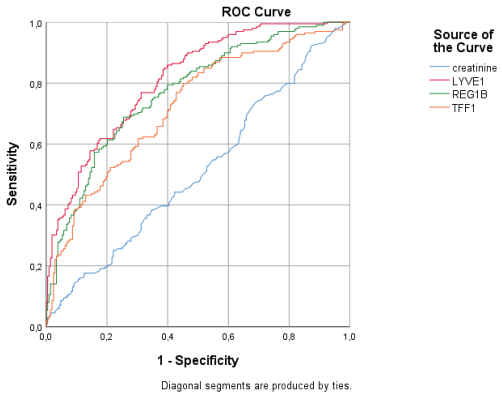

Figure 3. Graph of ROC analysis results for benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients

Table 5. Result of ROC analysis for combinations in benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients

Test result variable (s)	Area under the curve (AUC)
Creatinine	0.514
LYVE1	0.812
REG1B	0.771
TFF1	0.722

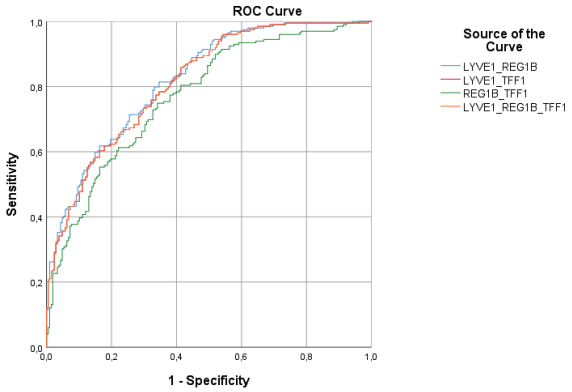

Figure 4. Graph of ROC analysis results for combinations in benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients

Table 6. Result of ROC analysis for combinations in benign hepatobiliary disease and pancreatic ductal adenocarcinoma patients

Test result variable (s)	Area under the curve (AUC)
LYVE1_REG1B	0.821
LYVE1_TFF1	0.814
REG1B_TFF1	0.77
LYVE1_REG1B_TFF1	0.814

Discussion

Pancreatic cancer is one of the deadliest types of cancer, with its incidence increasing day by day and having the lowest 5-year survival rate. The survival rate is so low that the 5-year rate is only 10% [16]. Furthermore, because pancreatic cancer is typically identified at an advanced stage, treatment choices are restricted, and the majority of patient's experience recurrence and metastasis following curative surgery. This enhances the disease's lethality. Recent breakthroughs in surgical procedures and several new chemotherapy regimens have not improved the disease's terrible prognosis [17,18]. PDAC, the most frequent kind of pancreatic cancer, is one of the deadliest tumors and has a poor prognosis compared to other types of pancreatic cancer [19]. Treatment options for this aggressive cancer type, which is most commonly identified at an advanced stage, are relatively restricted; occasionally surgery cannot be used, and it is confined to systemic chemotherapy with small clinical outcomes [20].

Therefore, there is a huge field of study for the diagnosis and treatment of this disease, which has such a high mortality rate and limited treatment strategies. Many studies have been conducted for this disease, however the markers and treatments found have not reached sufficient clinical level. Therefore, there is a great need for studies especially for the early diagnosis of the disease. Because the disease is not detected in the advanced stage and the mortality rate increases. However, if the disease is detected at an early stage and treatment is started as soon as possible, it has been reported in studies that the survival rate reaches 30%. Therefore, parameters that can be used as early stage biomarkers are important for the diagnosis of the disease.

DOI: 10.5455/medscience.2023.11.225

For this purpose, this study aims to examine the effects of PDAC-related proteins on the disease using an open access dataset. For this purpose, ROC analyses were performed with the mentioned proteins for the control and benign hepatobiliary disease patient groups and PDAC groups in the dataset. In addition, the combinations of the proteins included in the study (2-with and 3-with combinations) how their changes together will play a role in PDAC detection were also analysed. Thus, the effects of the combination of the parameters on PDAC will be determined instead of their single discrimination power.

When the statistical analysis results are examined, according to the double comparison results for the control-PDAC and benign hepatobiliary disease-PDAC groups, it can be stated that the other three variables, LYVE1, REG1B, TFF1, except the creatinine variable, show statistically significant differences between the groups.

According to the ROC analysis results for the control-PDAC and benign hepatobiliary disease-PDAC groups, the discriminatory power of the creatinine variable was found quite low between the groups ($AUC_{control\text{-}PDAC}$=0.531, $AUC_{benign\ hepatobiliary\ disease\text{-}PDAC}$=0.514, respectively).

The AUC values obtained from the ROC analysis results for the other variables LYVE1, REG1B, TFF1 in control-PDAC were 0.891, 0.810, 0.862, respectively. Likewise, from the ROC analysis results for benign hepatobiliary disease-PDAC, the AUC values obtained for the LYVE1, REG1B, TFF1 variables are 0.812, 0.771, 0.772, respectively. In light of the results, it can be noted that these three variables have discriminatory power between the groups. For both comparisons, the discriminatory power of the LYVE1 variable is higher than the other variables.

If the results of the ROC analysis performed by taking the combinations of the variables together are examined, the AUC values obtained for benign hepatobiliary disease-PDAC are 0.821 for LYVE1_REG1B, 0.814 for LYVE1_TFF1, 0.770 for REG1B_TFF1, while the AUC values obtained by taking the combination of all variables are 0.814 for LYVE1_REG1B_TFF1. According to these results, it can be concluded that taking combinations for benign hepatobiliary disease-PDAC comparison is not very effective. However, AUC values obtained by taking combinations for control-PDAC groups are 0.898 for LYVE1_REG1B, 0.905 for LYVE1_TFF1, 0.876 for REG1B_TFF1, while the AUC values obtained by taking combinations of all variables are 0.907 for LYVE1_REG1B_TFF1. According to these results, it was observed that taking combinations for control-PDAC groups produced better results than single ROC analysis. It is emphasized that the variable consisting of three combinations and the LYVE1_TFF1 variable pair discriminate highly (>0.90) especially for PDAC and control.

In the light of the findings obtained in the study, it can be concluded that ROC analysis results obtained with single variables have limited discrimination for PDAC, while ROC analysis results obtained from combinations are more determinative for PDAC. Therefore, evaluating the risk factors associated with the disease together in some cases will be valuable in terms of diagnosis. And it may increase the accuracy of diagnosis. Evaluation of these parameters for PDAC may be important for early diagnosis and early treatment may reduce mortality rates and increase survival rates.

Conclusion

In the light of the findings obtained in the study, it can be concluded that ROC analysis results obtained with single variables have limited discrimination for PDAC, while ROC analysis results obtained from combinations are more determinative for PDAC. Therefore, evaluating the risk factors associated with the disease together in some cases will be valuable in terms of diagnosis. And it may increase the accuracy of diagnosis. Evaluation of these parameters for PDAC may be important for early diagnosis and early treatment may reduce mortality rates and increase survival rates..

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Not necessary for this manuscript.

References

1. Howlader N, Noone A, Krapcho M, et al. eds. SEER Cancer statistics review, 1975–2017, National Cancer Institute. Bethesda, MD. 2020.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
3. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68:471-87.
4. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet. 2004;363:1049-57.
5. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395-406.
6. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200-10.
7. Danai LV, Babic A, Rosenthal MH, et al. Altered exocrine function can drive adipose wasting in early pancreatic cancer. Nature. 2018;558:600-4.
8. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes. 2017;66:1103-10.
9. Kays JK, Shahda S, Stanley M, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J Cachexia Sarcopenia Muscle. 2018;9:673-84.
10. He J, Blair AB, Groot VP, et al. Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer?. Ann Surg. 2018;268:1-8.
11. Van Cutsem E, Tempero MA, Sigal D, et al. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. J Clin Oncol. 2020;38:3185-94.

DOI: 10.5455/medscience.2023.11.225

12. Tempero M, Oh DY, Tabernero J, et al. Ibrutinib in combination with nab-paclitaxel and gemcitabine for first-line treatment of patients with metastatic pancreatic adenocarcinoma: phase III RESOLVE study. Ann Oncol. 2021;32:600-8.

13. Debernardi S, O'Brien H, Algahmdi AS, et al. A combination of urinary biomarker panel and PancRISK score for earlier detection of pancreatic cancer: a case-control study. PLoS Med. 2020;17:e1003489.

14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.

15. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol. 2012;3:105-19.

16. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.

17. O'Neil NJ, Bailey ML, Hieter P. Synthetic lethality and cancer. Nat Rev Genet. 2017;18:613-23.

18. Qian Y, Gong Y, Fan Z, et al. Molecular alterations and targeted therapy in pancreatic ductal adenocarcinoma. J Hematol Oncol. 2020;13:130.

19. Grossberg AJ, Chu LC, Deig CR, et al. Multidisciplinary standards of care and recent progress in pancreatic ductal adenocarcinoma. CA Cancer J Clin. 2020;70:375-403.

20. Hosein AN, Dougan SK, Aguirre AJ, Maitra A. Translational advances in pancreatic ductal adenocarcinoma therapy. Nat Cancer. 2022;3:272-86.